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Inflammatory Cytokines and Cardiovascular Disease

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Abstract: The designation of atherosclerosis as a chronic inflammatory process represents an interesting paradigmatic shift for cardiologists. The plasma concentrations of interleukin-6 and its hepatic byproduct, C-reactive protein, may reflect the intensity of occult plaque inflammation and the vulnerability to rupture. Monocyte chemoattractant protein-1 and interleukin-8 play a crucial role in initiating atherosclerosis by recruiting monocytes/macrophages to the vessel wall, which promotes atherosclerotic lesions and plaque vulnerability. In addition, circulating levels of these proinflammatory cytokines increase in patients with acute myocardial infarction and unstable angina, but not in those with stable angina. Also, the plasma concentrations of these cytokines increase after percutaneous coronary intervention, causing late restenosis after the procedure. Angiotensin II and other atherogenic factors induce these cytokines in the cardiovascular tissues through the activation of transcription factors, such as nuclear factor-κB or peroxisome proliferator-activated receptors. Conversely, HMG-CoA reductase inhibitors (statins) can potently inhibit these proinflammatory factors in the vessels. A small GTP-binding protein, Rho, may be a key molecule to explain the anti-inflammatory effects of statins. Interleukin-10 also exerts anti-inflammatory effects on the cardiovascular tissues, possibly by deactivating proinflammatory cytokines and inducible nitric oxide synthase. Gene therapy using interleukin-10 may be a promising means for untreatable or complicated cases of cardiovascular diseases. Thus, therapeutic modulations of these inflammatory cytokines may be useful in the prevention of atherosclerosis and future cardiovascular events.

Key words: acute coronary syndromes, CRP, statin, transcription factor.

INTRODUCTION

Many lines of evidence, ranging from *in vitro* experiments to epidemiologic studies, demonstrate that atherosclerosis is intrinsically an inflammatory disease characterized by inflammatory cell infiltration and cytokine expression [1]. An early step in atherogenesis involves monocyte adhesion to the endothelium and penetration into the subendothelial space. An enhanced expression of adhesion molecules and chemokines like monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8) accelerates this process, forming initial atherosclerotic lesions referred to as 'fatty streaks'. Activated monocytes/macrophages scavenge oxidized, low density lipoprotein (LDL) in the subendothelial space and change into foam cells. Accumulation of these cells and ambient vascular components produces proinflammatory cytokines and metalloproteinases in atheromas, resulting in atherosclerotic plaque ruptures. The plasma concentrations of interleukin-6 (IL-6) and its hepatic byproduct, C-reactive protein (CRP), may reflect the intensity of occult plaque inflammation and determine the vulnerability to rupture [2]. Acute coronary syndromes (ACS), including unstable angina and acute myocardial infarction (MI), occur as a clinical manifestation of the coronary plaque rupture (Fig. 1). In contrast, interleukin-10 (IL-10), a potent anti-inflammatory cytokine, may improve atherogenesis by counteracting the effects of these proinflammatory cytokines [3, 4]. In this review, we discuss the current concept of pathology and clinical utility of inflammation-related cytokines, IL-6, -8, -10, and MCP-1, in cardiovascular diseases.

INTERLEUKIN-6

Possible Signal Transduction and Cellular Effects

IL-6 is an important local and circulating marker of inflammation in cardiovascular tissues. IL-6 is a 26 kDa cytokine, produced by many types of cells, including lymphocytes, monocytes, fibroblasts, vascular smooth muscle cells (VSMCs), and endothelial cells (ECs). IL-6 stimulates the expression of tissue factor, matrix degrading enzymes, and LDL receptors in macrophages [5-8], as well as aggregation of platelets, proliferation of VSMCs [9, 10], and production of CRP by hepatocytes. IL-6 also enhances the expression of adhesion molecules and other cytokines in ECs, e.g., interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which potently enhance the inflammatory reaction [7,9].

Accumulating evidence shows that angiotensin II (Ang II) may exert a strong atherogenic effect by inducing IL-6 in VSMCs [11, 12]. Activation of Ang II type 1 receptor (AT1R) and nuclear factor-κB (NF-κB) may upregulate IL-6 expression in VSMCs [11, 13]. NF-κB is a key transcription factor that enhances inflammatory response in the vascular cells. Moreover, the promoter regions of the IL-6 gene contain the binding sequences for NF-κB. Thus, Ang II may induce IL-6 expression possibly through AT1R and subsequent NF-κB activation (Fig. 2).

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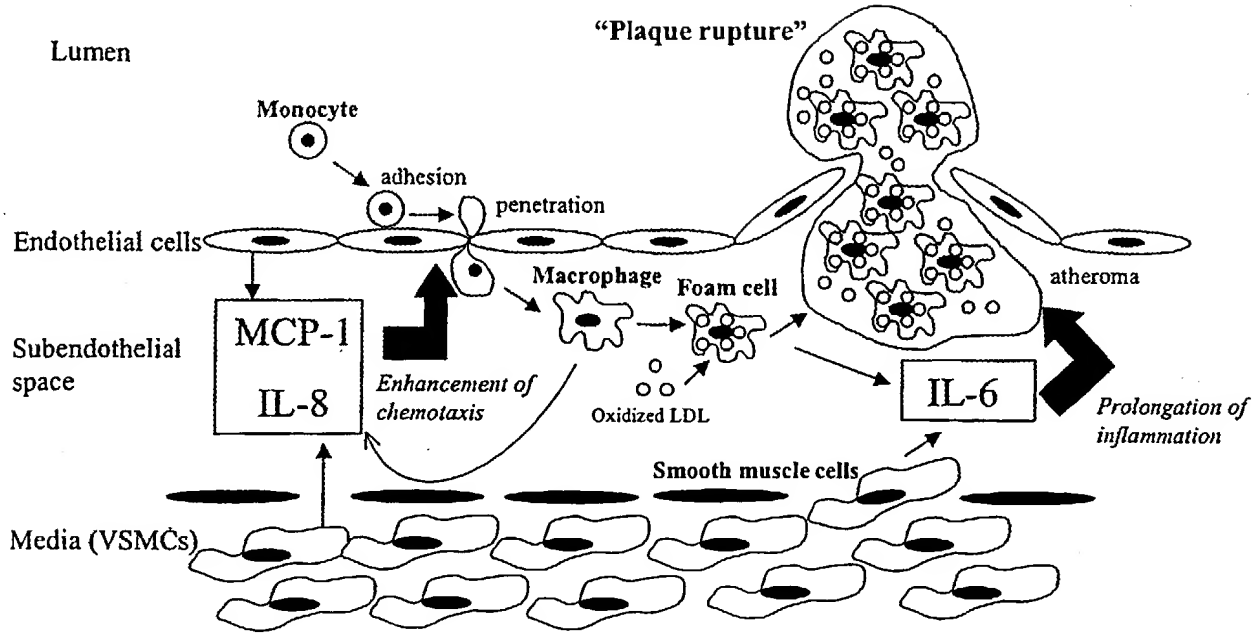

Fig. (1). Effects of proinflammatory cytokines on atherogenesis

Inflammatory cell infiltration and cytokine expression may accelerate atherogenesis. An early step in atherogenesis involves monocyte adhesion to the endothelium and penetration into the subendothelial space. MCP-1 and IL-8 enhance this process. Activated monocytes/macrophages scavenge oxidized-LDL in the subendothelial space and change into foam cells. Accumulation of these cells and vascular smooth muscle cells may produce proinflammatory cytokines like IL-6, resulting in atherosclerotic plaque ruptures. MCP-1 indicates monocyte chemoattractant protein-1; IL, interleukin; LDL, low-density lipoprotein.

Many clinical and experimental studies have revealed that HMG-CoA reductase inhibitors (statins) can exert many cholesterol-independent, cardioprotective actions. These effects of statins are referred to as 'pleiotropic effects' and include regulation of proinflammatory cytokines and nitric oxide (NO) expression in macrophages, ECs, and VSMCs [14-16]. Since these effects of statins were reversed by addition of geranyl-geranyl pyrophosphate (GGPP), decreased GGPP and subsequent inhibition of Rho may be important process in these pleiotropic effects. Rho is a small GTP-binding protein that can be post-translationally modified by GGPP, causing various cellular effects through mRNA stabilization and regulation of transcription factors [17]. We reported that lipophilic statins, but not hydrophilic pravastatin, attenuate IL-6 expression in human VSMCs partially through GGPP or Rho inhibition [18]. We also demonstrated that statins decrease Ang II-induced IL-6 expression in VSMCs [19]. However, the effects of statins on the renin-angiotensin system remained unclear until Ichiki *et al.* [20] addressed this issue. They reported that lipophilic statins directly downregulate AT1R expression in VSMCs in a GGPP and Rho-dependent manner. Lipophilic statins also attenuate the calcium response of VSMCs to Ang II. In contrast, hydrophilic pravastatin did not show these changes. These results suggest that an AT1R-GGPP-Rho pathway may be crucial in the pleiotropic effects of lipophilic statins (Fig. 3).

Of the members of the nuclear-receptor family of ligand-activated transcription factors, there are 3 known peroxisome proliferator-activated receptor (PPAR) forms: gamma (γ), alpha (α), and delta (δ). Staels *et al.* [21] showed that

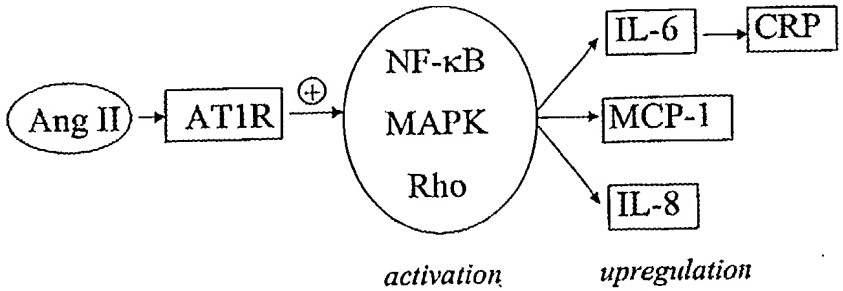

Fig. (2). Effects of angiotensin II on proinflammatory signals in vascular cells

Angiotensin II (Ang II) may exert a strong atherogenic effect through upregulation of proinflammatory cytokines like IL-6, -8, and MCP-1 in vascular cells. These effects are mediated by AT1R and subsequent activation of NF-κB, MAPK, and Rho. CRP, hepatic byproduct of IL-6, is a useful marker for vascular inflammation. Ang II indicates angiotensin II; AT1R, Ang II type I receptor; NF-κB, nuclear factor-κB; MAPK, mitogen-activated protein kinase; CRP, C-reactive protein.

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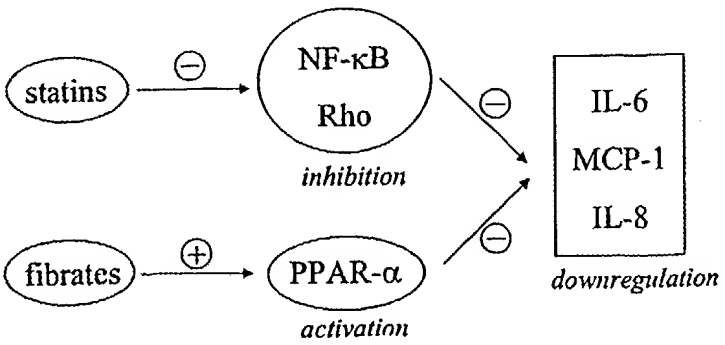

Fig. (3). Effects of statins and fibrates on proinflammatory signals in vascular cells

HMG-CoA reductase inhibitors (statins) and fibrates attenuate atherogenesis not only through lipid-lowering effects but also through downregulation of proinflammatory cytokines like IL-6, -8, and MCP-1. Statins inhibit NF-κB and Rho, but fibrates activate PPAR-α, resulting in the decrease of these cytokine expression. PPAR indicates peroxisome proliferator-activated receptor.

PPAR-α is expressed in human VSMCs, which participate in plaque formation and post-angioplasty restenosis. PPAR-α ligands, but not PPAR-γ ligands, inhibit IL-1-induced IL-6 production in VSMCs. In hyperlipidemic patients, treatment with the PPAR-α ligand fenofibrate decreases the plasma concentrations of IL-6, fibrinogen and CRP [21]. Thus, PPAR-α activators may improve atherosclerosis and restenosis by reducing the inflammatory response in VSMCs and the concentration of plasma acute-phase proteins (Fig. 3). In contrast, the activation of PPAR-γ does not inhibit the IL-6 or TNF-α production by macrophages stimulated with lipopolysaccharide (LPS) *in vitro* and *in vivo* [22].

Clinical Implication

Elevated levels of IL-6 are associated with unfavorable short- and long-term prognoses in patient with coronary artery disease [23]. We previously reported for the first time that circulating IL-6 levels increase in patients with acute MI [24]. The extent of IL-6 increase was not associated with the infarction size indicated by creatine kinase assay, while maximal IL-6 levels were correlated with maximal CRP levels [24]. The source of circulating IL-6 at the early stage of MI may be coronary atherosclerotic lesions [25-27] and cardiac myocytes [24]. Immunohistochemically, IL-6 accumulated at the shoulder region of coronary atherosclerotic plaques, where the plaque rupture predominantly occurs [28], along with cardiac myocytes and infiltrating mononuclear cells in the viable border zone of MI in a canine reperfusion model [29].

In addition to MI, IL-6 levels also increase in unstable angina [30, 31]. We reported that plasma IL-6 levels in patients with unstable angina were significantly higher than those with stable angina or in control subjects [32].

Moreover, increased IL-6 levels on admission were associated with a complicated hospital course. In contrast, Biasucci *et al.* [33] reported that a drop in IL-6 level 48 hours after admission can predict an uneventful hospital course in patients with unstable angina. Lindmark *et al.* [34] demonstrated that IL-6 is a strong independent marker of mortality in unstable angina and effectively identifies patients who benefit most from an early invasive treatment.

Also, elevated IL-6 levels may reflect the instability of stenotic lesions after percutaneous coronary intervention (PCI). We reported that elevated IL-6 concentrations in coronary sinus after elective PCI correlates with the future restenosis in patients with stable angina [35, 36]. The source of this increase was the heart itself; IL-6 concentrations in the peripheral arterial blood samples taken at the same time were not increased.

Large-scale clinical studies also support the clinical utility of IL-6 as a marker for coronary artery disease. In a prospective study involving 14,916 apparently healthy men, Ridker *et al.* [23] compared the baseline plasma IL-6 of 202 participants who subsequently developed MI with that of 202 participants matched for age and smoking status who did not develop vascular disease during a 6-year follow-up. Median IL-6 levels at the baseline of the former group were higher than those of the latter. The risk of future MI increased with increasing quartiles of baseline IL-6 levels to the extent that men in the highest quartile at entry had a relative risk 2.3-fold higher than those in the lowest quartile.

Also, the concentrations of the inflammatory marker CRP increase in patients with ACS. Higher CRP concentrations can predict a worse outcome [37], as observed in IL-6. Interestingly, the protective effects of aspirin [38] and statins [39] are greatest in cases with the highest baseline CRP concentrations, indicating the anti-inflammatory properties of both the drug classes [40]. Ikonomidis *et al.* [41] reported that patients with unstable angina had more than twice the median IL-6 levels compared to controls, and 6-week aspirin treatment decreased the IL-6 levels. Bickel *et al.* [42] examined the anti-inflammatory effects of statins in 950 patients with coronary artery disease. They found that the plasma IL-6 levels of patients with statin therapy were significantly lower than those without the lipid-lowering drug therapy, although lipid status was not different between them. In addition, Chan *et al.* [43] reported that atorvastatin therapy decreased plasma IL-6 levels in subjects with visceral obesity. These findings suggest that IL-6 reduction is the therapeutic mechanism of aspirin or statins in patients with coronary artery disease.

MONOCYTE CHEMOATTRACTANT PROTEIN-1

Possible Signal Transduction and Cellular Effects

MCP-1, a monomeric polypeptide of molecular weight 9 to 15 kDa, is the prototype of the C-C chemokine β subfamily with powerful activity toward monocytes. MCP-1

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rapidly causes rolling monocytes to adhere firmly onto ECs expressing E-selectin, and infiltrate into the subendothelial space [44]. In addition to the recruitment and activation of monocytes, MCP-1 induces the expression of tissue factor [45], superoxide anions, and proinflammatory genes. Various stimuli enhance the production of MCP-1 by VSMCs, ECs, and macrophages. Cytokines [46], minimally modified LDL [47], Ang II [48], homocysteine [49], shear stress [50], thrombin [51], and activated platelets induce MCP-1 expression in these cells.

The p38 mitogen-activated protein kinase (MAPK) and NF-κB may play a critical role in MCP-1 expression in ECs and VSMCs (Fig. 2). Marin *et al.* [51] reported that p38 MAPK inhibitor SB203580, but not p42/p44 MAPK inhibitor PD98059, decreased thrombin-induced MCP-1 production by human umbilical vein endothelial cells (HUVECs). Also, SB203580 inhibits the induction of MCP-1 by thrombin receptor-1 agonist in these cells, suggesting functional links between the thrombin G protein-coupled receptor and the p38 MAPK pathway. Kilgore *et al.* [52] demonstrated that activation of complement cascade increases MCP-1 expression in HUVECs through cytosolic to nuclear translocation of NF-κB. Lysophosphatidylcholine (LPC), enriched in oxidized LDL, also induces MCP-1 gene expression in rat VSMCs [53]. Promoter analysis of MCP-1 indicated that LPC-responsive elements in the MCP-1 gene involve MAPK, a tyrosine kinase, and a protein kinase C.

Statins, through the inhibition of NF-κB activity, reduce MCP-1 expression in VSMCs, ECs, and monocytes/macrophages *in vitro* (Fig. 3) [54, 55] . Bustos *et al.* [56] induced atherosclerosis in the femoral arteries of rabbits by endothelial damage and atherogenic diet. Treatment with atorvastatin decreased the arterial macrophage infiltration, MCP-1 expression, and NF-κB activity in this animal model.

The effects of PPARs on MCP-1 expression have also been reported. Pasceri *et al.* [57] reported that the PPAR-α activation with fenofibrate and a synthetic ligand, Wy 14649, almost completely abolished the CRP-induced MCP-1 expression in HUVECs, while the PPAR-γ activator ciglitazone had only a moderate effect. Conversely, Lee *et al.* [58] reported that Wy14643 increased MCP-1 synthesis by human aortic ECs. In addition, a PPAR-γ activator, troglitazone, decreased the MCP-1 levels. The effects of PPARs on MCP-1 production are still controversial.

Clinical Implications

Many studies have shown clinical significance of MCP-1 in plaque formation and rupture. MCP-1 expression in macrophages promotes atherosclerosis by increasing both macrophage numbers and oxidized lipid accumulation in apo E-deficient mice [59]. We previously reported that MCP-1 mRNA increases in atherosclerotic arteries of patients undergoing coronary bypass revascularization [60]. Studies using *in situ* hybridization also demonstrated the enhanced accumulation of MCP-1 mRNA in the macrophage-rich, thrombotic, and necrotic lesions of human atherosclerosis, although no MCP-1 mRNA was found in sublesional medial smooth muscle cells or in normal arteries [61]. An immunohistochemical study during autopsies revealed that ECs and subendothelial macrophages are the major sources of MCP-1 in early atherosclerotic lesions [62]. First, ECs express MCP-1 to cause the initial influx of monocytes into the subendothelial space [44]. Then, infiltrated monocytes/macrophages express MCP-1 to continue the influx of monocytes into the plaque. Additionally, MCP-1 may play a key role in reperfusion injury. MCP-1 increases in infiltrating cells and small veins of the reperfused canine myocardium [63]. The number of MCP-1 mRNA-positive macrophages peaked at 3 hours after reperfusion [64].

Circulating MCP-1 levels increase in patients with ACS [32]. In patients with MI, plasma MCP-1 levels began to increase 3 hours after the onset of chest pain, and remained elevated during a 24-hour observation period [65]. The circulating monocytes in patients with unstable angina were activated to express high plasma levels of MCP-1 [66]. Indeed, the plasma levels of both MCP-1 [32, 67] and tissue factor [68] were higher in patients with ACS than in those with stable angina. A positive correlation between the plasma MCP-1 and tissue factor levels suggests that enhanced coagulability by MCP-1 may also promote the thrombotic complications in ACS.

Moreover, MCP-1 plays a pathogenic role in the restenosis after PCI. MCP-1 mRNA was rapidly induced in pig iliac arteries after de-endothelialization [69]. In patients with stable angina, the plasma MCP-1 levels at 48 hours and 3 months after elective PCI were higher in the restenosis group than those in the non-restenosis group [70]. The plasma MCP-1 levels before and after PCI were also higher in patients with restenosis than those without restenosis [71].

A blockade of MCP-1 expression may be a useful strategy against atherosclerosis and coronary artery disease. Neutralization of MCP-1 with anti-MCP-1 antibody inhibits neointimal hyperplasia in rat carotid arterial injury [72]. Egashira *et al.* [73] devised a new strategy for anti-MCP-1 gene therapy against arteriosclerosis using an N-terminal deletion mutant of the MCP-1 gene. The mutant binds to the MCP-1 receptor CCR2, but blocks MCP-1-mediated monocyte chemotaxis. Ni *et al.* [74] transferred this deletion mutant into the skeletal muscle of apo E-deficient mice. This strategy effectively blocked the MCP-1 activity and formation of atherosclerotic lesions without changing the serum lipid concentrations. These studies show that interfering with a single chemokine may have a dramatic effect on disease progression.

Statins may provide clinical benefits for patients with atherosclerosis through the anti-MCP-1 effect. A study using a mouse air-pouch model of local inflammation showed that an oral administration of lovastatin and pravastatin reduced the LPS-induced leukocyte recruitment and exudated the MCP-1 production [75]. Rezaie-Majd *et al.* [76] reported that 6-week treatment with simvastatin decreased serum MCP-1 levels of hypercholesterolemic patients. Also, lipophilic statins decreased MCP-1 mRNA in cultured HUVECs and peripheral blood mononuclear cells from the patients and the normolipidemic subjects. The effects of statins on MCP-1 regulation through non-lipid mechanism may provide new explanations for their beneficial impact on mortality and morbidity in cardiovascular patients [77].

Prostaglandins have been evaluated primarily for the treatment of patients with critical leg ischemia. Martin *et al.*

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[78] reported that prostaglandin (PG) E_1 inhibited LPS-induced MCP-1 expression in murine macrophage cell lines through a partial inhibition of a cAMP-mediated pathway. We showed that the serum MCP-1 levels were increased in patients with peripheral arterial disease (PAD) compared with control subjects. Also, one-week parenteral administration of PGE_1 decreased the serum MCP-1 levels in these patients [79].

INTERLEUKIN-8

Possible Signal Transduction and Cellular Effects

IL-8 is a monocyte/macrophage-derived CXC chemokine that recruits neutrophils to sites of inflammation. IL-8 also triggers firm adhesion of rolling monocytes to vascular endothelium and infiltration of the vessel wall, leading to the earliest step of atherosclerosis [80]. IL-8 activates both CXCR1 and CXCR2 on microvascular endothelial cells. However, activation of CXCR2 may contribute to the increased vascular permeability observed in acute inflammation [81]. IL-8 receptor CXCR2 is strongly expressed on macrophages in atherosclerotic lesions [82]. Mice lacking IL-8 receptors are less susceptible to atherosclerosis with fewer monocytes in vascular lesions [83]. In addition to monocyte recruitment, IL-8 also plays an important role as a mitogen and chemoattractant factor for VSMCs [84]. Moreover, IL-8 may induce rupture of atheromatous plaques through its angiogenic properties, because IL-8 mRNA expression and corneal neovascular response in specimens from patients after coronary atherectomy significantly increased compared with those from control subjects [85].

Cholesterol-loading macrophages prominently induce IL-8 expression in human coronary atheromas [86]. Proinflammatory cytokines like IL-1 and TNF-α upregulate IL-8 expression in monocytes/macrophages [86, 87]. Fu *et al.* [88] reported that deoxy-delta12, 14 prostaglandin J2 (15d-PGJ2), a natural ligand for activation of PPAR-γ, also increased IL-8 gene expression in THP-1 macrophages. Since MAPK inhibitor PD98059 or antioxidant and NF-κB inhibitor pyrrolidine dithiocarbamate markedly inhibited the 15d-PGJ2-induced IL-8 upregulation, a MAPK- NF-κB pathway may be crucial for IL-8 regulation in macrophages. Mechanical strain also induces IL-8 expression in monocytes/macrophages. We recently reported that cyclic mechanical strain at 1 Hz for 6 hours upregulated IL-8 expression in human monocytic cells by DNA microarray analysis [89].

Histamine, LPS, and TNF-α upregulate IL-8 expression in human coronary ECs with activation of NF-κB [90]. Homocysteine and the dominant negative IκB mutants inhibit TNF-α-induced IL-8 expression in HUVECs with a decrease in NF-κB activation [91, 92]. However, a p38MAPK inhibitor, SB203580, inhibited thrombin-induced IL-8 expression in HUVECs [51]. Moreover, active p38MAPK and Rho-dependent signaling may regulate LPS-induced IL-8 expression and NF-κB activation in HUVECs [93]. These results suggest that a Rho-MAPK- NF-κB pathway is also crucial for IL-8 expression in ECs.

Autocrine secretion of IL-8 by VSMCs may enhance the migration and proliferation of the cells, leading to the stenotic lesion of the vessels [94]. Cultured VSMCs can constitutively produce IL-8. IL-1 and TNF-α upregulate IL-8 expression in human VSMCs [94, 95]. We recently reported that Ang II increases IL-8 levels in cultured human VSMCs possibly through AT1R activation [96]. Accumulating evidence shows that Ang II may exert a remarkable atherogenic effect by inducing proinflammatory cytokines in VSMCs [11, 54]. Upregulation of these cytokines by Ang II is mediated by the activation of AT1R and NF-κB. The promoter regions of the IL-8 gene contain binding sequences for NF-κB. In addition, NF-κB activation is required for TNF-α-induced IL-8 expression in human VSMCs [94]. Thus, Ang II may induce IL-8 expression in VSMCs possibly through AT1R and subsequent NF-κB activation (Fig. 2).

Similar to IL-6, we reported that lipophilic statins, but not hydrophilic pravastatin, attenuate IL-8 expression in human VSMCs. These effects occur partially through decreased GGPP or Rho inhibition [18, 96]. It has also been reported that hydrophilic pravastatin decreases IL-8 expression in human ECs through inhibition of Ras and activator protein-1 (AP-1) [97]. These differences in signal transduction may be explained by differences in cell types or stimuli; however, further studies are required to clarify these issues.

Clinical Implications

IL-8 expression is enhanced in patients with atherosclerotic diseases, such as ACS, abdominal aortic aneurysms (AAA), and PAD. Serum IL-8 levels are significantly higher in patients with ACS than those in healthy controls [98]. IL-8 levels of infarct-related coronary artery samples from patients with ACS are higher than those from patients with stable angina, using a transluminal extraction catheter [99]. Furthermore, plasma IL-8 levels after PCI increased in patients with ACS, but not in those with stable angina [100]. These results suggest that increased levels of circulating IL-8 may reflect local vascular inflammation trigged by IL-8 in patients with ACS. By using a membrane-based complementary DNA expression array, it was found that IL-8 gene products of human AAA tissues increase compared with those of normal aortas [101]. In patients with PAD, serum IL-8 levels are also elevated compared with those of healthy controls, before and after an acute exercise test [102]. Along with IL-6 and MCP-1, IL-8 may play a critical role as a predictive and prognostic marker of atherosclerotic diseases.

Recent studies have shown that statin therapy downregulates IL-8 expression in patients with atherosclerosis and hypercholesterolemia. IL-8 mRNA accumulation in peripheral blood mononuclear cells of hypercholesterolemic patients increases compared with that of control subjects [103]. Treatment with simvastatin decreases serum IL-8 levels and IL-8 mRNA expression in monocytes from the hypercholesterolemic patients after 6 weeks compared with baseline values [76]. Interestingly, statin-induced IL-8 downregulation showed a significant additional decrease after 6 months, while cholesterol levels showed only a slight additional decrease. These results suggest different molecular mechanisms between statin-induced cytokine regulation and cholesterol reduction.

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INTERLEUKIN-10

Possible Signal Transduction and Cellular Effects

IL-10 is an endogenous, potent anti-inflammatory cytokine. During inflammatory processes in vivo, monocytes/macrophages and T cells produce IL-10 to limit the burst of proinflammatory mediators released by the same cells. An imbalance between T helper type 1 (Th1) and 2 (Th2) cells may cause immune dysfunction and ongoing inflammatory response in vascular tissues. IL-10 is a Th2-associated cytokine that may augment humoral immunity and lower the inflammatory response through inhibition of Th1 cells, monocytes/macrophages, and proinflammatory cytokines. IL-10 also inhibits TNF-α-induced MCP-1 expression in cardiomyocytes [104] and IL-8 expression in monocytes [105]. These immunosuppressive and anti-inflammatory effects of IL-10 have been shown in patients with systemic inflammation like transplanted organ rejection [106], immune complex diseases, and sepsis [107].

Functional IL-10 receptor (IL-10R) complexes are tetramers consisting of two IL-10R1 polypeptide chains and two IL-10R2 chains. Binding of IL-10 to the extracellular domain of IL-10R1 activates phosphorylation of the receptor-associated Janus tyrosine kinases (JAKs). These kinases phosphorylate specific tyrosine residues on the intracellular domain of the IL-10R1 chain. Once phosphorylated, these tyrosine residues serve as temporary docking sites for the latent transcription factor STAT3 (signal transducer and activator of transcription-3). STAT3 translocates to the nucleus where it binds to promoters of various IL-10-responsive genes. One of these genes, SOCS-3 (suppressor of cytokine signaling-3) is a member of newly identified genes that inhibit JAK/STAT-dependent signaling. IL-10 inhibits LPS-induced TNF-α expression in monocytes/macrophages through the rapid synthesis of SOCS-3 [108] and the inhibition of the IL-10R-JAK-STAT pathway [109-112]. In contrast, forced expression of SOCS-3 significantly suppresses the ability of IL-10 to trigger tyrosine phosphorylation of STAT3 [113]. Therefore, SOCS-3 functions both as an LPS signal inhibitor and as a negative feedback regulator of IL-10/STAT3 signaling in monocytes/macrophages (Fig. 4). In neutrophils, however, the role of IL-10/STAT signaling in SOCS-3 induction is controversial [114, 115].

NF-κB and MAPK pathways may also be important for the anti-inflammatory action of IL-10. IL-10 blocks the NF-κB activation in macrophages induced by LPS, TNF-α, and reactive oxygen species [116,117]. In human monocytes, IL-10 suppresses LPS-induced cyclooxgenase-2 expression by inhibiting the phosphorylation of p38MAPK and extracellular signal-regulated kinase (ERK) 2 [118]. In contrast, the p38MAPK pathway, but not the p42/44MAPK and ERK pathway, is involved in the LPS-induced IL-10 expression in human monocytic cells [119, 120].

Clinical Implications

Current evidence suggests a potential cardioprotective role of IL-10 in the pathological conditions, such as myocardial injury, atherosclerosis, restenosis after PCI, and myocarditis. Ischemia/reperfusion (I/R) is a well-known stimulus for acute inflammatory response in myocardial injury, leading to cell death and impaired pump function. Plasma IL-10 concentrations increase in patients with myocardial I/R [121, 122]. Exogenous administration of IL-10 attenuates the myocardial I/R injury and in vitro adherence of neutrophils to vascular endothelium in rats [123]. Studies using IL-10-deficient mice demonstrated that endogenously produced IL-10 is critical in diminishing myocardial injury after myocardial I/R [124, 125]. In addition, plasma nitric oxide (NO) levels significantly increased in IL-10-deficient mice after reperfusion, compared with those of the wild type. These results indicate that IL-10 deficiency may attenuate cardioprotective effects through augmentation of inducible NO synthase (iNOS), the possible proinflammatory isoform of NOS. In fact, many studies have reported that expression of iNOS and the subsequent production of NO increased in the late phase of reperfusion.

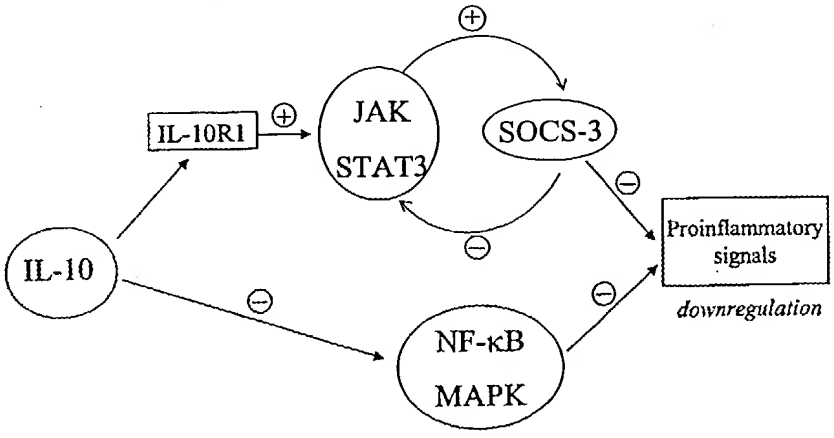

Fig. (4). Anti-inflammatory signals of IL-10 in monocytes/macrophages

IL-10 downregulates proinflammatory signals in monocytes/macrophages through both activation of IL-10R1-JAK/STAT-SOCS-3 and inhibition of NF-κB and MAPK pathways. SOCS-3 also functions as a negative feedback regulator of IL-10/STAT3 signaling. IL-10R1 indicates IL-10 type 1 receptor; JAK, Janus tyrosine kinase; STAT3, signal transducer and activator of transcription-3; SOCS-3, suppressor of cytokine signaling-3.

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Enhanced expression of iNOS also impaired constrictor responses of the carotid artery after LPS stimulation in IL-10-deficient mice [126]. In contrast, Jones *et al.* [125] suggested that the cardioprotective effects of IL-10 are not dependent on the presence of iNOS.

Higher levels of IL-10 may protect the events in ACS by stabilizing local inflammation of atherosclerotic plaques. In patients with unstable angina, lower serum levels of IL-10 on admission can predict the increased rate of cardiovascular events [127]. The IL-10 genotype may influence the risk for cardiovascular events in hemodialysis patients [128]. In advanced human atherosclerotic plaques, enhancement of IL-10 reactively occurs in macrophages and VSMCs [129]. Consistent with its anti-inflammatory properties, higher levels of IL-10 expression significantly decrease iNOS expression and cell death. In atherosclerotic lesions of IL-10-deficient mice with hyperlipidemic diet, IL-10 downregulation correlates with activation of T cells and proinflammatory cytokines. Conversely, both pretreatment of ECs with recombinant IL-10 and transfection of the cells with adenovirus expressing IL-10 can inhibit monocyte-endothelium interaction [130]. In addition, overexpression of IL-10 in transgenic mice decreases atherosclerotic lesions compared with those of wild-type or IL-10-deficient mice [130]. These results strongly suggest the possible anti-atherogenic effects of local IL-10 induction in the vascular tissues.

In hypercholesterolemic rabbits during PCI, treatment with recombinant human IL-10 markedly reduced macrophage infiltration and intimal hyperplasia [131]. Exogenous IL-10 also inhibits TNF-α-induced VSMC proliferation [132]. In addition, endogenous IL-10 decreased superoxide anion production in blood vessels induced by LPS, preventing the impairment of endothelium-dependent relaxation [133]. These effects of IL-10 may improve restenosis after PCI by attenuating endothelial dysfunction and VSMC proliferation.

Treatment with IL-10 also improves experimental autoimmune and viral myocarditis. The direct injection of plasmid vector expressing murine IL-10 cDNA into the rat muscle improved the 21-day survival rate and hemodynamic parameter, and reduced myocardial lesions in experimental autoimmune myocarditis [134]. Recombinant human IL-10, which is fully active on mouse cells, was also effective in a murine model of acute viral myocarditis [135]. This treatment improved the 14-day survival rate and myocardial lesions with a decrease in TNF-α and iNOS expression. We recently reported that adeno-associated virus (AAV)-mediated IL-10 gene transfer inhibits atherosclerosis in apoE-deficient mice through suppression of MCP-1 expression [136]. These results provide new insights into the in vivo effects of IL-10; however, further studies are required for the optimal delivery means of IL-10 targeting human cardiovascular protection.

CONCLUSION

The designation of atherosclerosis as a chronic inflammatory process represents an interesting and logical paradigmatic shift for cardiologists. The plasma concentrations of IL-6, -8, and MCP-1 may reflect the intensity of local vascular inflammation, and predict the incidence of ACS and restenosis after PCI. Molecular biology has revealed that the therapeutic modulation of these proinflammatory cytokines may be a promising strategy for cardiovascular protection. Anti-inflammatory effects of IL-10 may also provide an alternative for the therapy of complicated cases. However, further studies are required to elucidate the relationship between cytokine regulation and other important atherogenic factors like growth hormones, lipid mediators, and mechanical stress. We should also compile enough data on the comparison of anti-inflammation therapy with the established lipid-lowering or anti-hypertensive therapy. After evaluation of the harm and effectiveness, cytokine modulator therapy may contribute to the control of atherosclerotic diseases.

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